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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/002,491	11/15/2001	Brett P. Monia	RTS-0239	2236

7590 10/27/2004

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EXAMINER	
MCGARRY, SEAN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/002,491	MONIA ET AL.	
	Examiner	Art Unit	
	Sean R McGarry	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2004*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10 and 12-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-10 and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

SUPPLEMENTAL DETAILED ACTION

The instant action is mailed in response to a telephone inquiry from applicants representative which inquired about the rejection under 37U.S.C. 102(b) over Evens [US 6,005,086]. It was asserted that there did not appear to be a SEQ ID NO 43 which corresponds to residues 1358-1373 of SEQ ID NO: 3 of the instant application. It was noted that the rejection appeared to be in error and a supplemental rejection would be mailed. Applicants inquiry was made within the first month of receiving the Official Action and the delay in providing the supplemental action is regretted.

The following action supercedes the Official Action mailed 4/28/04.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Stinchcomb et al [US 5,817,796].

Stinchcomb et al disclose ribozymes with 2'-5' linked adenylate residues. It is disclosed (see claims 1-3, for example) such ribozymes targeted to SEQ ID NO: 962 and 964 which correspond to residues 1454-1469 of instant SEQ ID NO: 3. The claimed

ribozymes meet all the structural requirements of the instant claims and are therefore, without evidence to the contrary, assumed to inherently posses the recited activity.

MPEP 2112.01:

PRODUCT AND APPARATUS CLAIMS X WHEN THE STRUCTURE RECITED IN THE REFERENCE IS SUBSTANTIALLY IDENTICAL TO THAT OF THE CLAIMS, CLAIMED PROPERTIES OR FUNCTIONS ARE PRESUMED TO BE INHERENT

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). AWhen the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.≅ *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433.

Claims 1 and 2 are rejected under 35 U.S.C. 102(e) and 102(a) as being anticipated by BEGER et al [WO 01/70982].

Beger et al disclose SEQ ID NO: 43 which corresponds to residues 1358-1373 of instant SEQ ID NO: 3. The oligonucleotide meets all the structural requirements of the instant claims and are therefore, without, evidence to the contrary, assumed to inherently posses the recited activity.

MPEP 2112.01:

PRODUCT AND APPARATUS CLAIMS X WHEN THE STRUCTURE RECITED IN THE REFERENCE IS SUBSTANTIALLY IDENTICAL TO THAT OF THE CLAIMS, CLAIMED PROPERTIES OR FUNCTIONS ARE PRESUMED TO BE INHERENT

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). AWhen the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.≅ *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433.

Claims 1, 2, 4-10, and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Forman et al [US 2002/0132223 A1] in view of Bennett et al [5,998,148] and Baracchini et al [5,801,154] and applicants admission at page 79 of the specification.

The claims have been amended to recite the limitation "nucleobases 534-1711 of a coding region of a nucleic acid encoding FXR (SEQ ID NO:3)". It is noted that this range essentially defines the coding region of human FXR SEQ ID NO:3, (see Table 1, for example.

Forman et al have taught the association of FXR expression and cardiovascular disease and disclose the importance of inhibiting the activity of expression of FXR. It is disclosed throughout the specification methods of screening for inhibitors and specifically disclose the use of antisense or ribozymes to inhibit the activity of FXR at column 11 paragraph 0108. Forman et al do not specifically disclose antisense within the range of 8 to 50 nucleobases, modification of internucleoside linkages such as phosphorothioate, modification of sugar moieties such as 2'-o-methoxyethyl, modification of nucleobases such as 5-methylcytosine, "chimeric" antisense

oligonucleotides, targeting an "active site", or compositions that comprise an FXR antisense with a pharmaceutically acceptable carrier such as a colloidal dispersion system. However, the following references clearly show that these limitations were routinely used in the prior art for optimization of antisense applications.

Bennett et al have taught general targeting guidelines at columns 3-4, for example. It has been taught to target 5' untranslated regions, start codons, coding regions, and 3'untranslated regions of a desired target, for example. It has been taught in column 5, for example, that antisense compounds are commonly used as research reagents and diagnostics, for example. At column 5 it has been taught that antisense oligonucleotides 8-30 nucleotides in length are particularly preferred. At columns 6-7 it has been taught preferred antisense oligonucleotides contain modified internucleoside linkages including phosphorothioate linkages, for example. At columns 7-8 it has been taught that preferred antisense oligonucleotides comprise modified sugar moieties including 2'-O-methoxyethyl. It has also been taught to modify nucleobases in antisense oligonucleotides at column 8-9 which includes the teaching of 5-methyl cytosine and at column 10 it has been taught chimeric antisense oligonucleotides. All of the above referred to modification are known in the art to provide beneficial attributes to antisense oligonucleotides such as increased hybridization and nuclease protection, for example. At columns 10-24, for example it has been taught numerous "carriers" for antisense oligonucleotides. In table I it has been taught the successful targeting of those regions taught in columns 3-4 with chimeric phosphorothioate oligonucleotides having 2'-MOE (a 2'-O-methoxyethyl modification).

Baracchini et al have taught, at column 6 for example, that antisense oligonucleotides can be used for research purposes and have also taught at column 6 that antisense oligonucleotides can be modified in their sugars, backbone linkages and nucleobases and that such modifications are desirable in antisense since these modifications have desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid targets and increases stability in the presence of nucleases. Baracchini et al provide specific examples of such modifications at columns 6-8 and in Example 1, for example. These specific examples taught by Baracchini et al include phosphorothioate linkages, 2'-O-methoxyethyl sugars, 5-methylcytosine and chimeric oligonucleotides, for example. Tables 1-4 show the successful design and use of modified oligonucleotides in cells in culture, for example. Table I therefore reflects the successful practice of general antisense design taught at columns 8-10, for example. At column 9 it has been taught that the "coding region" of a target nucleic acid may be effectively targeted by antisense compounds. At column 4, it has been taught various carriers for antisense delivery. It has been taught at column 8 that antisense are preferably 8 to 30 nucleotides and that it is more preferable to make antisense oligonucleotides that are 12 to 25 nucleotides in length, for example.

At page 79 of the specification it is admitted that the sequence of SEQ ID NO: 3 FXR was a published and known sequence of human FXR.

The prior art has therefore made the claimed invention obvious. The prior art has clearly disclosed to inhibit FXR via antisense or ribozymes and has also taught all of the limitations recited in the instant claims and taught the benefits of those limitations in

antisense applications, for example. The prior art has also show that by following general teachings one in the art can expect to find an antisense that will inhibit a target in cells in culture, for example. The prior art clearly teaches one in the art to target a coding region as is exemplified in the two patent references of record. The limitation "active site" is an empirically found target site where an antisense will be active in inhibiting a target and once one in the art selects an antisense as taught by the prior art they have also found an active site since an active antisense by virtue of its activity binds an "active site", for example.

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Applicant's arguments with respect to the pending claims have been considered but are moot in view of the new ground(s) of rejection. The new grounds of rejection take into consideration the new limitations entered by amendments filed 2/23/04. It is noted that the new rejection clearly set forth the target sequence (SEQ ID NO: 3) and teachings for targeting "coding regions" of a target nucleic acid, for example.

Any rejection of record not repeated in this Official Action is withdrawn.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SRM

SEAN McGARRY
PRIMARY EXAMINER